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US 20040267129 A1

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(54) Abstract Title: **Pulsed Ultrasound Imaging**

(57) A method of ultrasound imaging exploits the fact that short ultrasound bursts with a frequency much higher than a bubble resonance frequency (f_r) can excite the bubble to resonate at f_r if the burst is repeated at a frequency equal or close to f_r. Thus, ultrasound contrast agent having a natural resonance frequency of f_r is deployed within a target object. The target object is irradiated with an ultrasound excitation signal having a signal frequency much higher than f_r and comprising a series of bursts at a pulse repetition frequency sufficiently close to f_r to effect resonant behaviour in the contrast agent. A response is obtaining from the contrast agent indicative of the resonant behaviour.

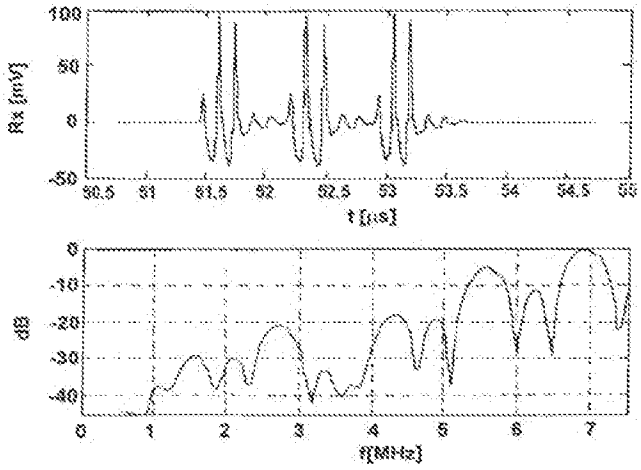

Fig. 4

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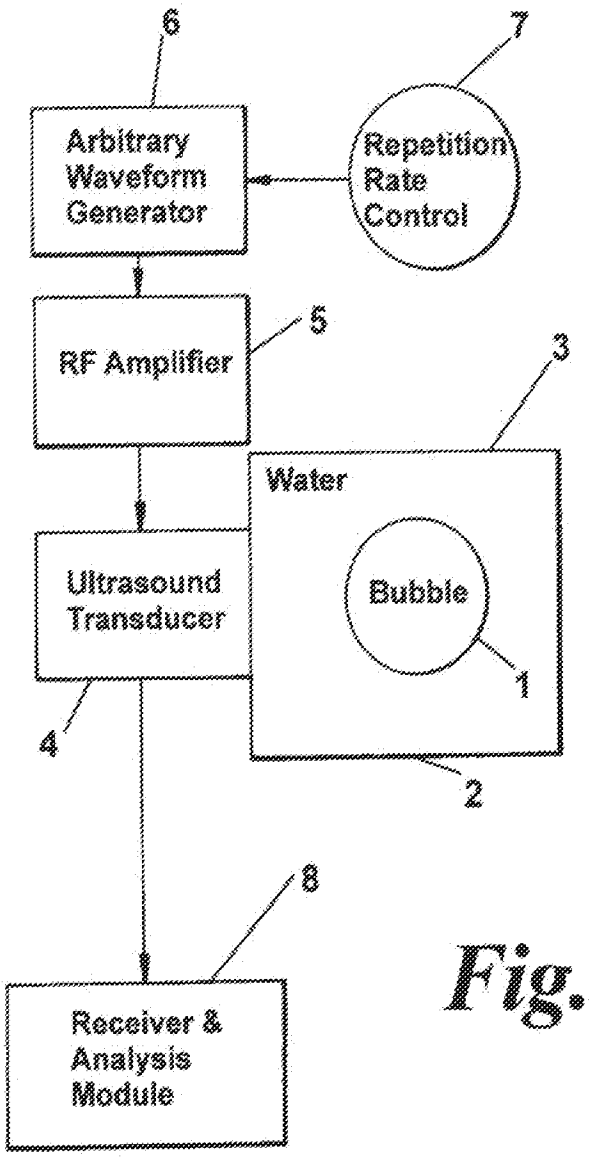

6
7
Arbitrary Waveform Generator
Repetition Rate Control
RF Amplifier
5
3
Water
Ultrasound Transducer
Bubble
1
4
2
8
Receiver & Analysis Module

Fig. 1(a)

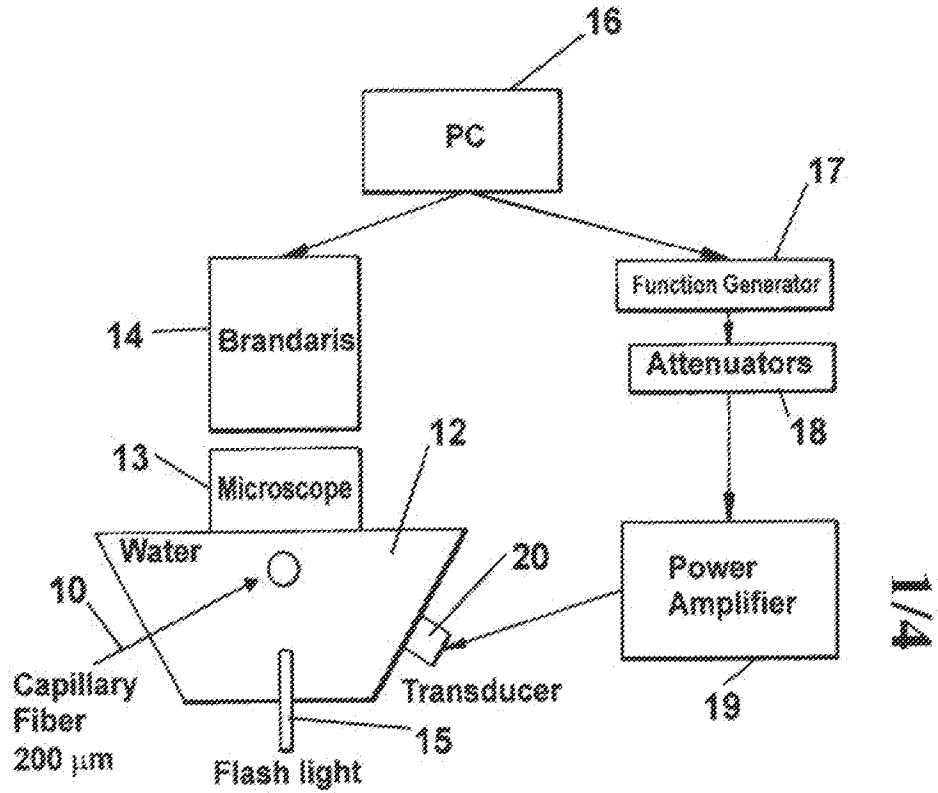
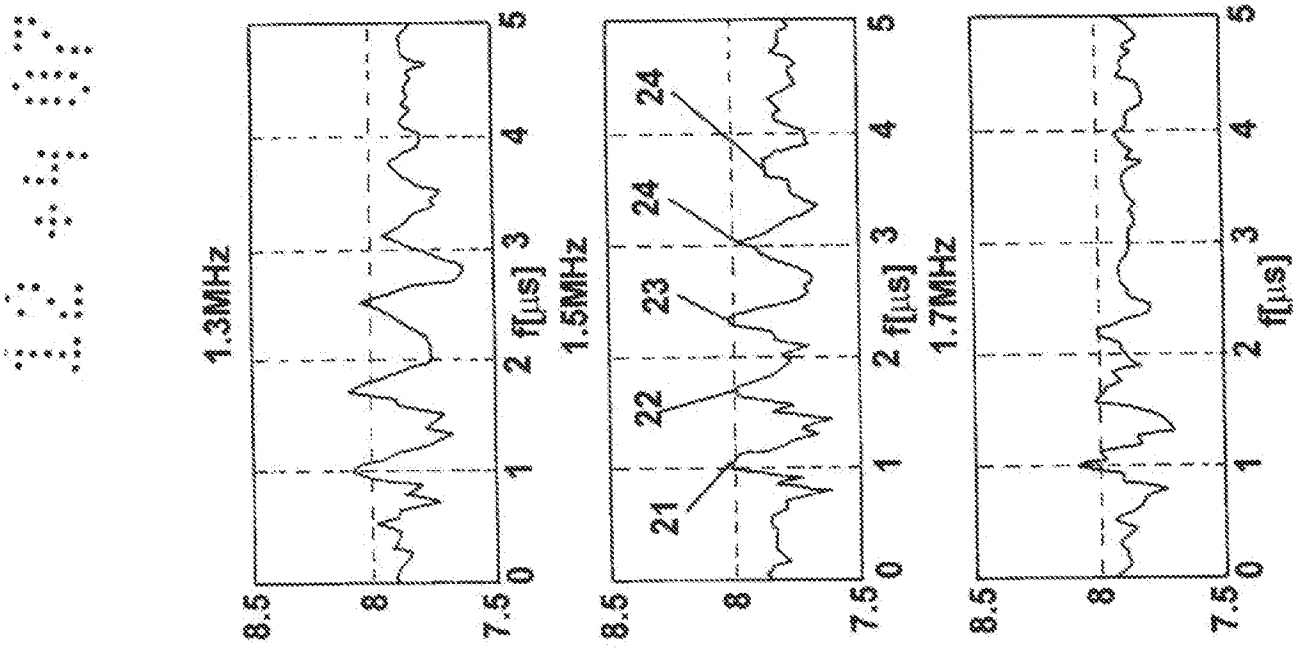

16
PC
17
Function Generator
14
Brandaris
Attenuators
18
13
Microscope
12
Water
20
10
Power Amplifier
Capillary Fiber 200 μm
Transducer
19
15
Flash light

Fig. 1(b)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1.4MHz
1.5MHz
1.6MHz
1.7MHz
1.8MHz
8.5
8
7.5
0
1
2
3
4
5
f[µs]
21
22
23
24

Fig. 2

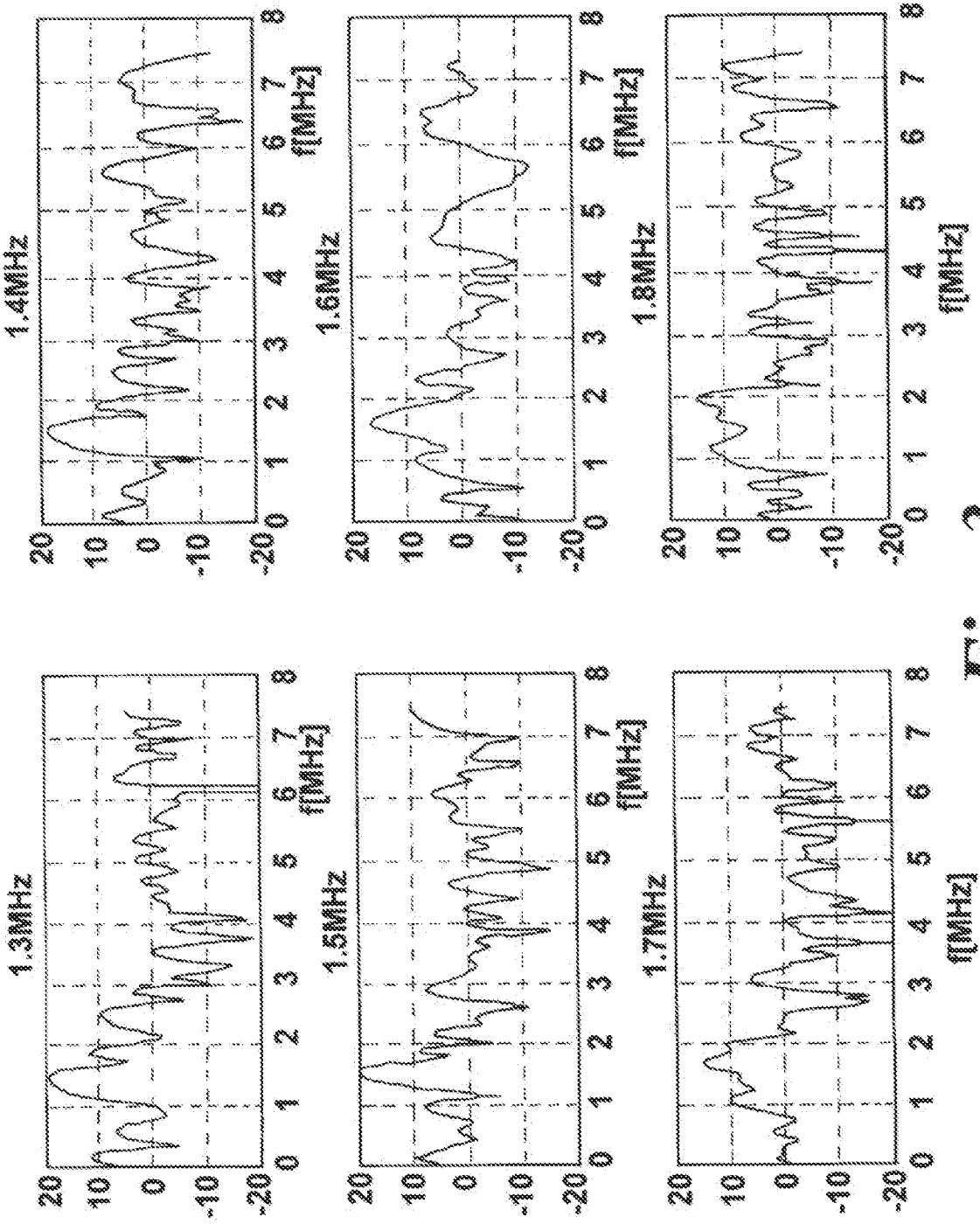

1.4MHz
1.6MHz
1.8MHz
1.3MHz
1.5MHz
1.7MHz
f[MHz]
20
10
0
-10
-20
0 1 2 3 4 5 6 7 8

Fig. 3

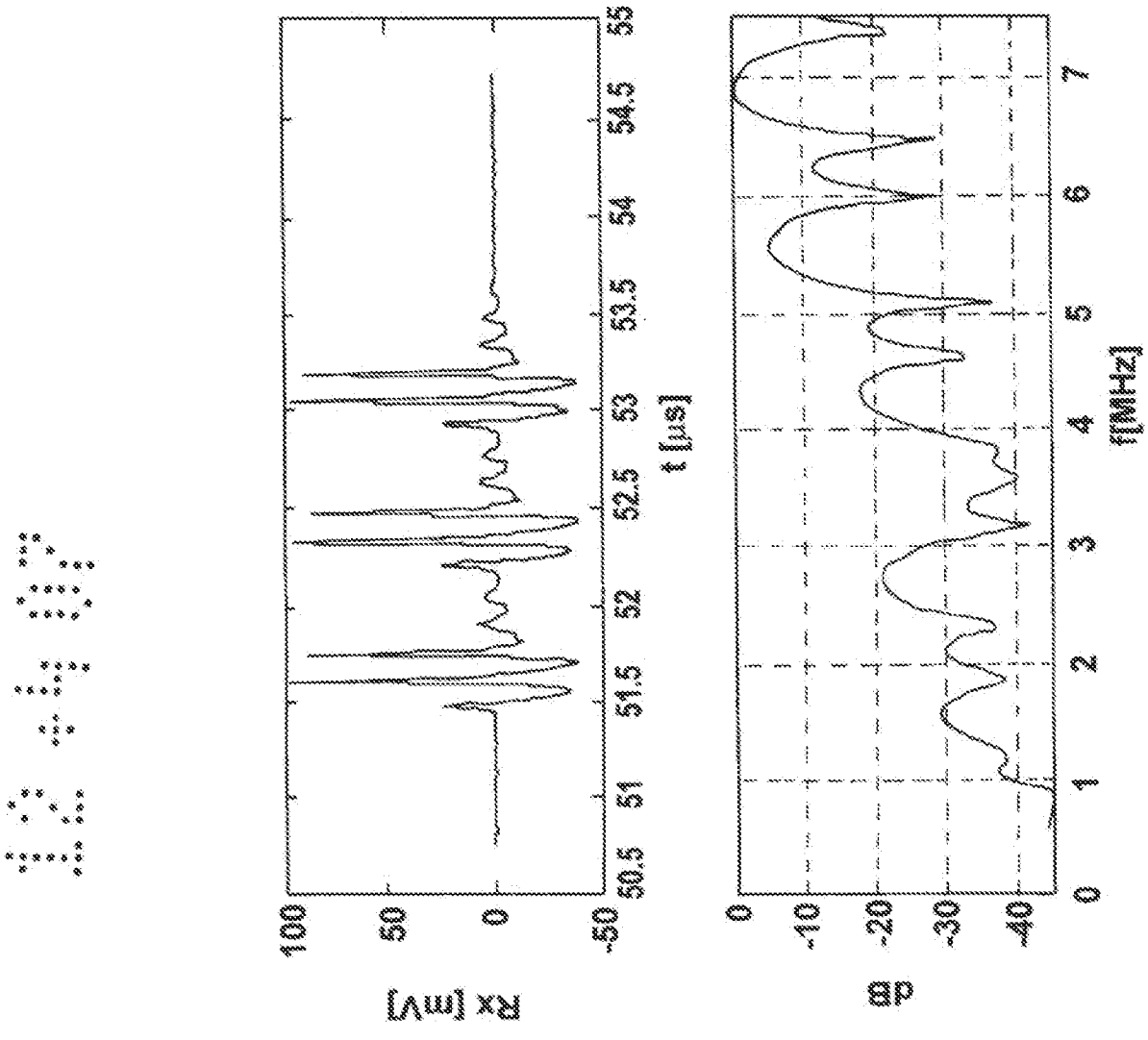

Rx [mV]
100
50
0
-50
50.5
51
51.5
52
52.5
53
53.5
54
54.5
55
t [µs]
dB
0
-10
-20
-30
-40
0
1
2
3
4
5
6
7
f[MHz]

Fig. 4

PULSE REPETITION RATE EXCITATION OF CONTRAST MATERIAL

The present invention relates to ultrasound detection and imaging techniques and in particular to methods for improving the effectiveness of contrast agents such as microbubbles used in various ultrasound imaging environments.

Gaseous bubbles in a liquid scatter ultrasound most efficiently when the transmission frequency of the excitation transducer is approximately equal to the damped oscillation frequency of the bubbles. This property is conventionally exploited in e.g. medical diagnostic ultrasound, where ultrasound contrast agents enhance the ultrasound backscatter from the regions where these bubbles are located. Typically, the bubbles may consist of small (1 – 4 micron diameter) gas bubbles stabilized by an albumin or phospholipids shell. The backscattered ultrasound signal is collected and, after processing the raw data into an image, the areas with enhanced backscatter are emphasised, thus facilitating e.g. blood pool measurements and blood vessel detection.

Furthermore, resonant behaviour (in which acoustic energy is locally stored and released with delay by acoustical radiation) is absent in tissue, but present in bubbles, resulting in a selection mechanism for enhanced bubble detection, resulting in a high contrast-to-tissue ratio, CTR.

Some medical applications, like intravascular ultrasound (IVUS) or micro emboli detection in the human brain, are limited to frequencies much higher than the resonance frequencies (f_r) of the bubbles to be detected. This limitation results in a poor backscatter of the ultrasound burst by the bubbles, decreasing the CTR. The resonance frequency of a gaseous bubble is proportional to the reciprocal of the radius of the bubble, so decreasing the average radius of bubbles in a contrast agent might overcome this limitation. However, in practice, smaller bubbles have the disadvantage of reduced backscatter efficiency, because the backscatter efficiency of a resonant bubble decreases as a function of the squared radius. Decreasing the transmit frequency to the resonance frequency of the bubbles generally leads to

lower axial resolution because the resolution-limiting wavelength depends on the reciprocal of the frequency.

It is therefore an object of the invention to overcome or mitigate the problems associated with the desire to use ultrasound excitation frequencies significantly higher than the resonance frequency of the bubbles.

In the prior art, WO 9115999 describes bubble imaging systems that rely on non-linear behaviour of bubbles to receive ultrasound signals at other than the transmit (excitation) frequencies, such as sub-harmonics and / or superharmonics, radiated by bubbles in response to excitation signals.

C-Y Wu and J Tsao: "The ultrasonic weak short-pulse responses of microbubbles based on a two-frequency approximation", Journal of the Acoustical Society of America, 2003, **114**(5), pp 2662-2671 described a system in which the non-linear behaviour of bubbles has been exploited by a dual-frequency approach, in which the beat frequency of two carrier waves (which is very much less than the transmit frequencies) is re-radiated by a population of bubbles and detected. That paper explicitly mentions that sub-harmonic or second harmonic responses are not responsible for the observed phenomena.

US 5833615 seeks to overcome the problem of small bubbles whose natural resonant frequency is not at the insonifying frequency by transiently increasing the size of the bubbles with excitation pulses from an excitation transducer so that imaging pulses from a second transducer are more effective.

WO9917808 describes a bubble recognition imaging system in which bubbles are irradiated by sequential single cycle pulses having a phase shift of 180 degrees. The interval between the two pulses is large enough to avoid influence of the first pulse on the radial response of the bubble to the second pulse. Due to the bubble nature, the bubble response will be different to the first and second (inverted) pulse. This difference can be processed to form an image in which regions with bubbles present are enhanced.

According to one aspect, the present invention provides a method of ultrasound imaging, comprising the steps of:

deploying ultrasound contrast agent having a natural resonance frequency of f_r within a target object;

irradiating the target object with an ultrasound excitation signal having a signal centre frequency much higher than f_r and comprising a series of bursts at a pulse repetition frequency sufficiently close to f_r to effect resonant behaviour in the contrast agent; and

obtaining a response from the contrast agent indicative of the resonant behaviour.

According to another aspect, the present invention provides apparatus for making ultrasound measurements on a target object comprising:

one or more transducers for transmitting ultrasound signals into, and receiving corresponding response signals from, the target object;

a signal generator adapted to (i) generate an excitation signal having a centre frequency f_0 and comprising a series of bursts at a pulse repetition frequency PRF_e much less than f_0, to initiate resonant behaviour in an ultrasound contrast agent in the target object, and (ii) generate an imaging signal adapted for the detection of resonance in the contrast agent at or near the frequency PRF_e; and

a receiver for detecting the existence of resonance in the contrast agent at or near the frequency PRF_e.

Embodiments of the present invention will now be described by way of example and with reference to the accompanying drawings in which:

Figure 1(a) is a schematic diagram of an ultrasound apparatus for excitation of contrast agent;

Figure 1(b) is a schematic diagram of a measurement system for verifying the effects described herein;

Figure 2 is a series of graphs showing the diameter of bubbles as a function of time when irradiated by an excitation beam having three bursts at varying pulse repetition frequencies at or close to the resonance frequency of the bubbles;

Figure 3 is a series of graphs showing the frequency spectra of the bubble radii corresponding to the time domain graphs of figure 2; and

Figure 4 is a pair of graphs showing the measured pressure burst of a 1.4 MHz pulse repetition rate excitation beam used for collection of the data shown in figure 2 and the corresponding frequency domain plot.

The invention exploits the fact that short ultrasound bursts with a frequency much higher than a bubble resonance frequency (f_r) can excite the bubble to resonate at f_r if the burst is repeated at a frequency equal or close to f_r. In an experimental example, it has been shown that by repeatedly transmitting high frequency (7 MHz) bursts at a pulse repetition frequency (PRF) approximately equal to the bubble resonance frequency, a 7.8 micron diameter bubble shows increasing radial excursion after subsequent bursts. This radial motion was captured by a fast-framing Brandaris-128 camera system, operating at about 15 mega frames per second (Mfps).

An ultrasound generation system suitable for implementing the invention is shown in figure 1(a) and a measurement system is shown in figure 1(b).

With reference to figure 1, a contrast agent gas bubble 1 is shown schematically contained within a suitable medium, e.g. water, in a vessel 3. The vessel 3 may, of course, represent any suitable target object on which ultrasound measurements may be made, such as the human body. An ultrasound transducer 4 provides an excitation beam for irradiating the target object 3 and may also provide means for receiving response signals therefrom. It will be understood that separate transducers could be used for excitation and response signals. The transducer 4 is driven by a signal generator comprising waveform generator 6 under control of a pulse rate controller 7. The signal generator output is fed to the ultrasound transducer 4 via amplifier 5.

For imaging and analysis, the received signals from transducer 4 are passed to a receiver and analysis module 8, the functions of which will be described in greater

detail later. The receiver and analysis module 8 generally may comprise suitable amplifiers, filters and digital signal processing systems.

With reference to figure 1(b), an experimental apparatus for determining the behaviour of the gas bubbles is now described. The observed gas bubbles were taken from an ultrasound contrast agent and were stabilized by a phospholipids monolayer shell, as described in J-M Gorce *et al*: "Influence of Bubble Size Distribution on the Echogenicity of Ultrasound Contrast Agents – A Study of SonoVue", 2000, Investigative Radiology 35(11): 661 - 671. The bubbles were reconstituted into emulsion with saline 4 to 12 days before the experiments.

The mix was injected into a capillary fibre 10 (Cuprophan, Akzo Nobel, Faser AG, Germany) with an outer diameter of 200 microns and a wall thickness of 25 microns, the fibre being housed in a suitable vessel 11 containing water 12. The fibre was optically and acoustically transparent. The fibre was positioned in the optical focus of a microscope 13 and camera system 14. The camera system 14, so-called Brandaris-128, consists of an array of 128 CCD cameras that acquire the image produced by the Olympus optical microscope 13. A fast-rotating mirror in the body of the camera system 14 sweeps the image over the subsequent CCD cameras, thus allowing for a very high frame rate of between 2 and 25 Mfps. A 1 cm diameter optical fibre leads the light of a xenon flash lamp 15 (EG&G FX-1163 Perkin–Elmer Optoelectronics, Salem, MA) close to the focal point. The camera hardware and mirror turbine is controlled by a computer system 16, which also control data acquisition and storage. An implementation of a circumference-tracking algorithm returns an estimate of the bubble radial motion as a function of time from the subsequent images captured by the CCD cameras.

In accordance with the general arrangement already described in connection with figure 1(a), an ultrasound burst was programmed into a Tabor arbitrary waveform generator 17 (Tabor 8026, Tel Hanan, Israel), which output was attenuated by a precision attenuator 18 (Agilent 355D, Palo Alto, CA) and amplified by a linear power amplifier 19 (ENI A-500RF). The transmit pulse was converted into ultrasound by a 10 MHz wideband single element focused transducer 20

(Panametrics V311, Olympus NDT, Waltham, MA), which was aligned to have its focus in the optical focus of the camera system. Pressures were measured in the independent water tank 11 using a calibrated needle hydrophone (200 micron diameter Precision Acoustics Ltd., Dorchester, Dorset, UK) which signal was captured by a Tektronix (TDS 3014B, Beaverton, Oregon, USA) digital oscilloscope at 5×10^6 samples per second (not shown).

Experimental results

A 7.8 micron diameter bubble was irradiated by an excitation signal having a signal centre frequency of 7 MHz and comprising bursts, each of two cycles duration, which bursts were repeated three times at a pulse repetition frequency ranging from 1.3 MHz to 1.8 MHz in steps of 0.1 MHz for respective exposures. The radial motion of the bubble and its Fourier transform for each of the exposures are shown in figures 2 and 3.

The first ultrasound burst arrives at 0.8 microseconds. The graphs show that the bubble oscillates with the excitation bursts, shown in figure 2 at peaks 21, 22, 23, which oscillations continue after the three excitation pulses, decaying over at least two cycles (peaks 24, 25) in at least the exposures corresponding to 1.3 MHz to 1.6 MHz (first four graphs). This resonant behaviour is almost absent at the 1.7 MHz and 1.8 MHz pulse repetition frequency exposures.

The increased frequency density resulting from the resonant behaviour is also shown in the Fourier transforms of the radius, in figure 3. The frequency density around the pulse repetition frequency is largest for a PRF of 1.5 MHz.

The transmission pressure burst for the 1.4 MHz pulse repetition frequency excitation signal and its frequency components are depicted in figure 4 as captured by the hydrophone in the focus of the transducer. Each of the bursts comprises two cycles and the bursts are separated by approximately 0.71 microseconds according to the repetition frequency of 1.4 MHz. The frequency spectrum was corrected for the hydrophone sensitivity. Here, it is clear that the power transmitted at 1.4 MHz is ~30 dB lower than at the excitation signal frequency of 7 MHz.

The invention uses the finding that bubbles can be put into resonance using frequencies other than the bubble resonance frequency. It is achieved by irradiation of bubbles with an ultrasound burst that is repeated at a pulse repetition frequency approximately equal to the resonance frequency of the bubbles.

This resonance effect, which is absent in tissue, may be used for enhanced discrimination between microbubbles and tissue. A number of techniques may be used to exploit this principle for imaging. In a most general aspect, once resonant behaviour has been induced in the contrast agent, any imaging strategy may be used which obtains a response from the contrast agent that is indicative of the resonant behaviour. This will distinguish over the non-contrast agent (e.g. tissue) in the target which will not have corresponding resonant behaviour induced therein.

A first exemplary imaging strategy uses a radial modulation approach, in which the bubbles are set into vibration by the excitation signals having bursts with pulse repetition frequency close to the resonance frequency of the bubbles. The excitation signals are then followed by at least two imaging signal bursts which are used to detect the difference in bubble behaviour during the resonance. Preferably, the imaging signal bursts have a pulse repetition frequency greater than the pulse repetition frequency of the excitation bursts, and more preferably at least double the pulse repetition frequency of the excitation bursts. Preferably, the imaging signal bursts have a signal frequency that is different from the centre frequency of the excitation signals so that the excitation signal bursts can be filtered out.

In one arrangement, the imaging signal examines the bubble in both its compression phase and in its expansion phase, i.e. the imaging signal bursts have a pulse repetition frequency of about twice that of the excitation signal pulse repetition frequency. In another arrangement, the imaging signal examines the echo or response signals received from the bubbles in a manner that will exploit the decaying resonance of the bubble radius after the excitation signal pulses. With further reference to figure 2, peaks 21, 22, 23 in bubble diameter correspond

to the three excitation signal pulses while peaks 24 and 25 correspond to resonance decay. Imaging signals reflected from the bubbles during peaks 24 and 25 will exhibit different responses due to stiffening of the bubble after excitation. Hence, the echo response of the bubbles from the two imaging bursts will show less correlation than any echo response originating from tissue or other non-resonant sources.

Therefore, preferably the imaging signal bursts are generated during a period immediately following the excitation signal bursts which period is of duration corresponding to at least two cycles of the excitation signal pulse repetition frequency in order to enable examination of the two decaying bubble oscillations following excitation. The imaging signal bursts may detect a change in the bubble diameters for two successive resonance periods during decay of the resonance following the excitation bursts. The imaging bursts may be generated interspersed between the excitation bursts. The imaging bursts may include an imaging burst prior to the excitation bursts. In general, the sequence of imaging bursts can partially or fully overlap the sequence of excitation bursts.

It will be understood that other excitation strategies may be used. Each burst may comprise 1 or more cycles of the excitation centre frequency sufficient to provide an impulse that will assist in generating resonant behaviour in the bubble, but sufficiently short to maintain separate bursts. The number of cycles in an excitation signal burst need not be a whole number, to allow for burst envelope shaping. Although the exemplary number of bursts in an excitation sequence is shown as three, more generally two or more bursts may be used provided that the objective of setting up measurable resonant behaviour in the bubbles is achieved. The interval between bursts (i.e. $1/PRF_e$) is sufficiently short that the influence of the first burst on the bubble radius is still present at the time of the radial response of the bubble to the second pulse. The excitation signal frequency is much higher than the pulse repetition frequency, which expression is intended to encompass at least a factor of more than two, preferably a factor of at least four, and more preferably a factor of at least six.

Preferably, each group of two or more excitation bursts is followed by a measuring interval without excitation bursts, in order to facilitate the imaging bursts and receiving of response signals therefrom. Preferably, the measuring interval is greater than the interval between the excitation bursts in a single series of excitation bursts (i.e. greater than the interval determined by the pulse repetition frequency PRF_e). More preferably, the measuring interval is greater than twice the interval between excitation bursts in a single series of excitation bursts in order to provide an imaging window sufficiently large to detect at least two resonance cycles in the bubbles (e.g. peaks 24, 25 of figure 2).

A second exemplary imaging strategy is based on two different imaging signals being transmitted: a primary imaging signal ('A(t)') having two short high-frequency pulses that are transmitted at an interval of $\tau = 1/PRF_e$ where PRF_e is the pulse repetition frequency of the excitation signal, and a secondary imaging signal ('B(t)') having only one such burst. The respective received response signals (A'(t) and B'(t)) are processed to form a composite signal, $C'(t) = A'(t) - B'(t) - B'(t - \tau)$, where τ is a time interval substantially equal to a time gap between the primary and secondary excitation signals. This signal C'(t) is zero in the case of tissue reflections, but non-zero in the case of bubble reflections, as the reflection of the second signal burst in signal A is different from that of $B(t - \tau)$. This principle can be used in sequences up to three cycles, as the ring down time is about two cycle periods.

A sequence of multiple excitation and imaging bursts may be repeated in order to form an image, at a sequence repetition frequency (SRF). The sequence interval time is $\tau_s = 1 / SRF$. Then, A(t) is transmitted at $t = 0$; B(t) is transmitted at τ_s; and the response $C'(t) = A'(t) - B'(t - \tau_s) - B'(t - \tau_s - \tau)$. In other words, the second (or last) received burst response in a two-burst (or multiple-burst) sequence will be different from a received response burst in a single-burst sequence. This difference is thought to be absent in response signals from tissue. Hence, by imaging the difference (compound signal C') only, the regions where bubbles are present are enhanced.

More generally, the second imaging approach allows for transmitting a primary imaging signal and one or more secondary imaging signals; receiving a corresponding plurality of responses from the bubbles respectively resulting from the primary and secondary imaging signals; generating an output signal comprising the difference between the response to the primary imaging signal and either

(i) the sum of the responses to the secondary imaging signals, or

(ii) the sum of the response to a single secondary imaging signal and one or more time-shifted copies of the response to the single secondary imaging signal, the time shift being substantially equal to a time gap between the primary and secondary imaging signals.

A third imaging approach records low-frequency signals from the target or region of interest in response to the excitation signals, i.e., the response at the pulse repetition frequency PRF_e. Although the excitation signal bursts contains frequency components equal to the PRF (see figure 4) the level is –30 dB compared to the burst centre frequency (–12 dB). This level might be sufficiently low compared to bubble transmitted levels at the PRF. The response signals from the bubbles are received and processed at a frequency corresponding to PRF_e.

Many variations in the techniques described above may be envisaged.

The phase of successive excitation bursts can be varied. The phase of the component of bubble radial oscillation occurring at the bubble resonant frequency will be sensitive to the phase of the high frequency excitation signal. For example, a high frequency burst with a significant positive pressure cycle leading will tend to induce a negative-going first radial excursion in the bubble. The opposite will occur for a negative pressure cycle. One phase modulation scheme would be as follows. The excitation signal sequence would consist of bursts that are inverted copies of each other. For example, the first excitation burst would have a positive-going pressure at the start of the first cycle, and the second burst would have a negative-going pressure at the start of its first cycle. To enhance resonant behaviour in the bubble, instead of a pulse repetition rate equal to the resonant frequency f_r, the pulse repetition rate will be 2 times f_r. This ensures that the

stimulation of resonant frequency radial excursions will be in an identical direction, and will therefore be constructive to the bubble resonance. By phase inverting alternate pulses the driving impulse for the radial excursions will be made in both the positive and negative going cycles of the radial oscillations. Thus, in a general sense, the expression "sufficiently close to f_r to effect resonant behaviour in the contrast agent" in respect of the excitation pulse repetition frequency encompasses a frequency of $2 f_r$ when appropriate adjustments to the phase of the excitation pulse signals is envisaged.

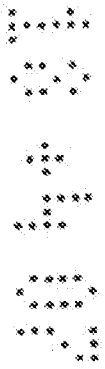
The amplitude of successive excitation bursts can also be varied. This enables exploitation of the amplitude dependence of bubble response to the excitation signal bursts. For example, asymmetric oscillations with more pronounced compressional excursions of the bubble radius may be induced. Both amplitude and phase modulations may be used within an excitation burst sequence. One example of this uses two alternating burst types, each burst separated by $1 / 2f_r$. One burst has a high amplitude with a positive pressure leading portion, which will tend to drive the bubble into compression, and is followed by a lower amplitude burst with negative pressure leading portion which will tend to drive the bubble into expansion.

Imaging signal bursts need not be used at all where it is possible to obtain a requisite response from the contrast agent simply from response to the excitation signals bursts.

Although the present invention has been described generally in the context of gaseous bubbles for contrast agent, it will be understood that the techniques are generally applicable for any contrast or other agent in which a resonant behaviour can be induced by the excitation signals. It will also be understood that gaseous bubbles in use as a contrast agent generally have a size distribution which results in a range of values of f_r for any given agent. It will be understood that the techniques described here may be used to cover such a distribution of resonant frequencies. Bubbles having an resonant frequency close to, but not exactly at, the excitation pulse repetition frequency may exhibit the requisite resonant response.

The excitation method generally described has applications in situations where bubble resonant frequencies are much lower than the imaging frequencies.

One application is the imaging of conventional (e.g. current clinically approved) microbubble contrast agents with higher frequencies. Specific situations include using intravascular ultrasound in clinical applications such as enhanced lumen boundary detection, vasa vasorum imaging, and targeted contrast agent detection for molecular imaging. Another application is in extracorporeal ultrasound biomicroscopy systems with applications for perfusion or molecular imaging in ophthalmology, dermatology or small animal (e.g. mouse, rat and rabbit) imaging. A third application is carotid artery imaging, which would also include the detection and quantification of carotid vasa vasorum. A fourth application would be prostate imaging, which may include microvascular detection for the purposes of detecting, diagnosing or therapeutic monitoring of tumours.



Non-contrast agent applications are also envisioned, such as the detection and characterization of gaseous micro-emboli. The latter application may for example be implemented in the context of transcranial ultrasound.

As discussed above, the general approach involves stimulating bubble oscillations near the bubble resonant frequencies using ultrasound pulses composed primarily or exclusively of frequencies far above the bubble resonant frequencies.

One scenario for this occurring is when a high frequency transmit transducer is capable of emitting a small amount of energy at the bubble resonant frequency. This energy can then be exploited with the described pulse sequences to contribute to stimulating bubble resonant frequency oscillations. Such an approach may be possible to implement on ultrasound systems with relatively simple signal generation architecture (i.e. those which do not allow for complex pulse sequences to be generated) such as some intravascular ultrasound systems.

A second scenario is when there is no transmitted energy at the bubble resonant frequency. Rather the transient oscillations following individual high frequency pulses can be amplified through the use of a specialized pulse sequences. It is recognized that the resulting transient oscillations at or near the bubble resonant frequency can be sensitive to the shape of the envelope and the pulse characteristics and that these can be manipulated and optimized to produce greater effects at the bubble oscillation frequency. This includes the specific shape, length and duration of the pulse envelopes, as well as the phase of the ultrasound centre frequency. Other excitation schemes are also considered, such as (but not limited to) frequency modulation or sweeping. Further, it is recognized that at sufficiently high pressures, ultrasound pulses centred at frequencies well above the bubble resonant frequency will produce asymmetric oscillations (i.e. compressional radial excursions are more pronounced) and that such asymmetries may be exploited to contribute to the bubble resonant frequency oscillations.

A third scenario, relevant to molecular imaging or bubbles in small capillaries, is when a bubble adjacent to a wall is induced, through radiation pressure effects, to undergo successive cycles of compression and rebound at the PRF. These bubble oscillations may involve shape oscillations (e.g. surface modes) and/or monopolar oscillations and/or translational oscillations. Such oscillations may radiate energy asymmetrically. These oscillations may also occur when dense layers of targeted bubbles are present. These resulting bubble oscillations in these situations may differ from free bubbles, and these differences may be a means by which to differentiate free and bound bubbles.

It is recognized that combinations of these mechanisms may be present and that the manner in which the imaging technique is implemented may vary depending on what can be implemented on a particular imaging system architecture or whether free or targeted bubbles are being imaged.

Other embodiments are intentionally within the scope of the accompanying claims.

CLAIMS

1. A method of ultrasound imaging, comprising the steps of:

deploying ultrasound contrast agent having a natural resonance frequency of f_r within a target object;

irradiating the target object with an ultrasound excitation signal having a signal centre frequency much higher than f_r and comprising a series of bursts at a pulse repetition frequency sufficiently close to f_r to effect resonant behaviour in the contrast agent; and

obtaining a response from the contrast agent indicative of the resonant behaviour.

2. The method of claim 1 in which the excitation signal bursts have a pulse repetition frequency less than or equal to $2f_r$.

3. The method of claim 1 in which the excitation signal comprises two or more successive bursts at the pulse repetition frequency, followed by a measuring interval greater than the interval determined by pulse repetition frequency.

4. The method of claim 3 in which the step of obtaining a response comprises irradiating the object with at least two imaging signal bursts during the measuring interval and receiving an echo response from said imaging bursts.

5. The method of claim 4 in which the imaging bursts have a signal centre frequency different from the signal centre frequency of the excitation bursts.

6. The method of claim 5 in which the step of obtaining a response further includes the step of filtering out received signals at the excitation signal centre frequency.

7. The method of claim 4 in which the pulse repetition frequency of the at least two imaging bursts is greater than the pulse repetition frequency of the excitation bursts.

8. The method of claim 7 in which the pulse repetition frequency of the at least two imaging bursts is at least double the pulse repetition frequency of the excitation bursts.

9. The method of claim 4 in which the imaging signal bursts are generated during a period immediately following the excitation signal bursts and of duration corresponding to at least two cycles of the excitation signal pulse repetition frequency.

10. The method of claim 4 in which the imaging signal bursts comprise a primary signal burst and one or more secondary signal bursts, further including the step of receiving a corresponding plurality of responses from the target object respectively resulting from the primary and secondary signal bursts and generating an output signal comprising the difference between the response to the primary signal burst and either

(i) the sum of the responses to the secondary signal bursts, or

(ii) the sum of the response to a single secondary signal burst and one or more time-shifted copies of the response to the single secondary signal burst , the time shift being substantially equal to a time gap between the primary and secondary signal bursts.

11. The method of claim 1 in which the step of obtaining a response comprises detecting received signals at a frequency corresponding to the pulse repetition rate.

12. The method of claim 1 further including irradiating the target object with a series of ultrasound imaging bursts at least partially or wholly overlapping the series of excitation bursts.

13. The method of claim 1 in which the excitation signal bursts in a series of bursts vary in phase.

14. The method of claim 1 in which the excitation signal bursts in a series of bursts vary in amplitude.

15. Apparatus for making ultrasound measurements on a target object comprising:

one or more transducers for transmitting ultrasound signals into, and receiving corresponding response signals from, the target object;

a signal generator adapted to (i) generate an excitation signal having a centre frequency f_0 and comprising a series of bursts at a pulse repetition frequency PRF_e much less than f_0, to initiate resonant behaviour in an ultrasound contrast agent in the target object, and (ii) generate an imaging signal adapted for the detection of resonance in the contrast agent at or near the frequency PRF_e; and

a receiver for detecting the existence of resonance in the contrast agent at or near the frequency PRF_e.

16. The apparatus of claim 15 in which the imaging signal is generated in a period immediately following said series of bursts.

17. The apparatus of claim 15 in which the signal generator is adapted to generate said excitation signal comprising two or more successive bursts at the pulse repetition frequency, followed by a measuring interval greater than $1/PRF_e$.

18. The apparatus of claim 17 in which the signal generator is adapted to generate at least two imaging signal bursts during the measuring interval, and the receiver is adapted to receive an echo response from said imaging bursts.

19. The apparatus of claim 18 in which the imaging bursts have a signal centre frequency different from the signal centre frequency of the excitation bursts.

20. The apparatus of claim 19 in which the receiver includes means for filtering out received signals at the excitation signal centre frequency, f_0.

21. The apparatus of claim 18 in which the signal generator is adapted to generate the at least two imaging bursts at a pulse repetition frequency greater than the pulse repetition frequency PRF_e of the excitation bursts.

22. The apparatus of claim 21 in which the signal generator is adapted to generate the at least two imaging bursts at a pulse repetition frequency at least double the pulse repetition frequency PRF_e of the excitation bursts.

23. The apparatus of claim 18 in which the signal generator is adapted to generate imaging signal bursts during said measuring interval of duration at least 2 x $1/PRF_e$.

24. The apparatus of claim 18 in which the signal generator is adapted to generate imaging signal bursts comprising a primary signal burst and one or more secondary signal bursts, and in which the receiver is adapted to receiving a corresponding plurality of responses from the target object respectively resulting from the primary and secondary signal bursts and generating an output signal comprising the difference between the response to the primary signal burst and either

(i) the sum of the responses to the secondary signal bursts, or

(ii) the sum of the response to a single secondary signal burst and one or more time-shifted copies of the response to the single secondary signal burst , the time shift being substantially equal to a time gap between the primary and secondary signal bursts.

25. Apparatus for making ultrasound measurements on a target object comprising:

one or more transducers for transmitting ultrasound signals into, and receiving corresponding response signals from, the target object;

a signal generator adapted to (i) generate an excitation signal having a frequency f_0 and comprising a series of bursts at a pulse repetition frequency PRF_e much less than f_0, to initiate resonant behaviour in an ultrasound contrast agent in the target object, and

a receiver for detecting the existence of resonance in the contrast agent at or near the frequency PRF_c.

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Application No:	GB0601380.9	**Examiner:**	Mr Mark Edwards
Claims searched:	1-25	**Date of search:**	25 May 2006

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
A		US5733527 A (SCHUTT) Columns 1 (lines 16-32), 2 (lines 26-44), 3 (lines 55-67), 4 (line 46) to 5 (line 19) & 8 (lines 53-67)
A		US6312383 B1 (LIZZI) Figure 5 and columns 1 (lines 36-47), 2 (lines 7-28 & 39-62), 3 (lines 7-40 & 47-67) & 5 (line 39) to 6 (line 24)
A		US2004/0267129 A1 (ANGELSEN) Paragraphs 5, 15, 19, 37-40 & 44-45

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{X}:

G1G

Worldwide search of patent documents classified in the following areas of the IPC

A61B; G01S

The following online and other databases have been used in the preparation of this search report

WPI, EPODOC, INSPEC, XPESP, XPIEE, XPI3E and the Internet